L Number	Hits	Search Text	DB	Time stamp
1	167	uromodulin	USPAT; US-PGPUB; EPO; JPO; DERWENT; USOCR	2004/03/04 15:08
2	135	uromodulin and kidney	USPAT; US-PGPUB; EPO; JPO; DERWENT; USOCR	2004/03/04 14:57
3	113	(uromodulin and kidney) AND TRANSGENIC	USPAT; US-PGPUB; EPO; JPO; DERWENT; USOCR	2004/03/04 14:57
4	7	XUE-RU	USPAT; US-PGPUB; EPO; JPO; DERWENT; USOCR	2004/03/04 14:59
5	45	sun NEAR tUNG$5	USPAT; US-PGPUB; EPO; JPO; DERWENT; USOCR	2004/03/04 15:02
6	23	sun NEAR tUNG-Tien	USPAT; US-PGPUB; EPO; JPO; DERWENT; USOCR	2004/03/04 15:02
7	104	uromodulin and (apical basal)	USPAT; US-PGPUB; EPO; JPO; DERWENT; USOCR	2004/03/04 15:05
10	0	apical NEAR surface NEAR membrane NEAR targeting	USPAT; US-PGPUB; EPO; JPO; DERWENT	2004/03/04 15:07
11	10	uromodulin and PIPLC	USPAT; US-PGPUB; EPO; JPO; DERWENT	2004/03/04 15:07
12	1	uromodulin NEAR promoter	USPAT; US-PGPUB; EPO; JPO; DERWENT; USOCR	2004/03/04 15:09
13	5	uromodulin SAME promoter	USPAT; US-PGPUB; EPO; JPO; DERWENT; USOCR	2004/03/04 15:09

(FILE 'HOME' ENTERED AT 15:12:07 ON 04 MAR 2004)

FILE 'MEDLINE, AGRICOLA, CANCERLIT, SCISEARCH, CAPLUS, MEDICONF' ENTERED AT 15:12:17 ON 04 MAR 2004

L1 15 S UROMODULIN PROMOTER
L2 7 DUP REM L1 (8 DUPLICATES REMOVED)

=> d an ti so au ab pi 7 6 5 4 3

L2 ANSWER 7 OF 7 CAPLUS COPYRIGHT 2004 ACS on STN
AN 2000:351690 CAPLUS
DN 133:13401
TI Transgenic animals as bioreactors for production of protein in urine by kidney-specific expression using the uromodulin gene promoter
SO PCT Int. Appl., 55 pp.
CODEN: PIXXD2
IN Wu, Xue-Ru; Sun, Tung-Tien
AB The invention relates to recombinant DNA constructs, a method for producing a recombinant biol. active protein in vivo in the urine of a non-human mammal using a kidney-specific promoter, such as the **uromodulin promoter**, and the transgenic non-human mammals that serve as urine-based bioreactors for protein production The recombinant DNA construct may also contain a secretion signal sequence operably linked to the heterologous gene. The method for producing a recombinant biol. active protein in vivo in the urine of a non-human mammal comprises the steps of introducing the recombinant DNA construct into a fertilized embryo to produce a transgenic non-human mammals expressing and secreting the protein in the urine, and collecting the urine to recover the protein. The **uromodulin promoter** is preferably of mouse, cattle, or rat, and the transgenic non-human mammal is goat, cow, sheep, pig, or horse. The nucleotide sequences of the mouse and goat uromodulin gene promoter region were obtained. Recombinant production of human growth hormone in the urine of transgenic mouse using the **uromodulin promoter** is described. (no data).

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2000029608	A1	20000525	WO 1999-US26870	19991112
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
EP 1135518	A1	20010926	EP 1999-958952	19991112
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				

L2 ANSWER 6 OF 7 MEDLINE on STN DUPLICATE 4
AN 2002361590 MEDLINE
TI **Uromodulin promoter** directs high-level expression of biologically active human alpha1-antitrypsin into mouse urine.
SO Biochemical journal, (2002 Jul 1) 365 (Pt 1) 7-11.
Journal code: 2984726R. ISSN: 0264-6021.
AU Zbikowska Halina M; Soukhareva Nadia; Behnam Reza; Lubon Henryk; Hammond David; Soukharev Serguei
AB We have recently shown that the regulatory sequence of the uromodulin gene, containing the 3.7 kb promoter, exon 1 and a part of exon 2, provided for kidney-specific expression of the reporter lacZ gene in transgenic mice [Zbikowska, Soukhareva, Behnam, Chang, Drews, Lubon, Hammond and Soukharev (2002) Transgenic Res., in the press]. In the present study, we generated transgenic mice harbouring the regulatory sequence of the uromodulin gene to direct the expression of human alpha1-antitrypsin (alpha1AT) into urine. Of the 13 founder mice that tested positive by PCR, seven showed the presence of the human protein in

their urine. The concentration of the recombinant human (rh) alpha1AT in the urine, estimated by using ELISA, ranged from 0.5 to 14 microg/ml in the F(0)-generation mice, and reached up to 65 microg/ml in the F1 generation. The transgenically produced rh alpha1AT was found to be N-glycosylated and biologically active. The N-terminal sequence analysis confirmed the identity of the human protein and revealed that the recombinant alpha1AT was correctly processed with the signal peptide cleaved off. Our results demonstrate for the first time that the uromodulin regulatory sequence provides a very attractive option for the potential large-scale production of functional therapeutic proteins in livestock.

L2 ANSWER 5 OF 7 MEDLINE on STN DUPLICATE 3
AN 2002452258 MEDLINE
TI The use of the **uromodulin promoter** to target production of recombinant proteins into urine of transgenic animals.
SO Transgenic research, (2002 Aug) 11 (4) 425-35.
Journal code: 9209120. ISSN: 0962-8819.
AU Zbikowska Halina M; Soukhareva Nadia; Behnam Reza; Chang Rosemary; Drews Roman; Lubon Henryk; Hammond David; Soukharev Serguei
AB A **uromodulin promoter** has been isolated, sequenced, and used to generate two sets of transgenic mice for expression of the lacZ marker gene and for production of the human recombinant erythropoietin (rhEPO) in urine. We demonstrated that the 5.6-kb fragment of the uromodulin gene containing the 3.7-kb promoter area and, both the first exon and part of the second exon, were sufficient to provide kidney-specific expression of the lacZ gene. Histological analysis of the lacZ expression pattern revealed beta-galactosidase activity specifically in the thick limb of Henle's loop. However, due to random integration of the transgene, ectopic expression was detected in some transgenic lines. Analysis of the EPO-transgenic mice showed that rhEPO was secreted into the urine of founder mice (up to 6 ng/ml). We were able to breed and analyze only two sublines with a very low expression level of rhEPO (up to 260 pg/ml). All of our transgenic mice expressing rhEPO in urine developed disease symptoms similar to polycythemia in humans. These included a considerable increase in red blood cell counts, hemoglobin concentration, and hematocrit concomitant with severe thrombocytopenia, all of which were detected in the rhEPO-expressing mice. Although our model did not prove to be beneficial for commercial production of rhEPO, we concluded that the **uromodulin promoter** could be useful for expression of other important therapeutic proteins into the urine of transgenic animals.

L2 ANSWER 4 OF 7 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN DUPLICATE 2
AN 2003:303452 SCISEARCH
TI Renal tubule-specific expression and urinary secretion of human growth hormone: a kidney-based transgenic bioreactor
SO TRANSGENIC RESEARCH, (APR 2003) Vol. 12, No. 2, pp. 155-162.
Publisher: KLUWER ACADEMIC PUBL, VAN GODEWIJCKSTRAAT 30, 3311 GZ DORDRECHT, NETHERLANDS.
ISSN: 0962-8819.
AU Zhu X H; Cheng J; Huang L W; Gao J; Zhang Z T; Pak J; Wu X R (Reprint)
AB Tissue-specific expression of human genes and secretion of human proteins into the body fluids in transgenic animals provides an important means of manufacturing large-quantity and high-quality pharmaceuticals. The present study demonstrates using transgenic mice that a 3.0 kb promoter of the mouse Tamm-Horsfall protein (THP, or uromodulin) gene directs the specific expression of human growth hormone (hGH) gene in the kidney followed by the secretion of hGH protein into the urine. hGH expression was detected in renal tubules that actively produce the THP, that is, the ascending limb of Henle's loop and distal convoluted tubules. Up to 500 ng/ml of hGH was detected in the urine, and this level remained constant throughout the 10-month observation period. hGH was also detectable in the stomach epithelium and serum in two of the transgenic lines, suggesting position-dependent effects of the transgene and leakage of hGH from the site of synthesis into the bloodstream, respectively. These results indicate that the 3.0 kb mouse THP promoter is primarily kidney-specific and can be used to convert kidney into a bioreactor in transgenic animals to produce recombinant proteins. Given the capacity of

urine production independent of age, sex and lactation, the ease of urinary protein purification, and the potentially distinct machinery for post-translational modifications in the kidney epithelial cells, the kidney-based transgenic bioreactor may offer unique opportunities for producing certain complex pharmaceuticals.

L2 ANSWER 3 OF 7 MEDLINE on STN DUPLICATE 1
AN 2003218484 MEDLINE
TI Kidney-specific activity of the bovine **uromodulin promoter**.
SO Transgenic research, (2003 Apr) 12 (2) 191-201.
Journal code: 9209120. ISSN: 0962-8819.
AU Kim Hun-Taek; Song In-Young; Piedrahita Jorge
AB A 10-kilobase (kb) lambda bacteriophage bovine genomic clone containing 5.4 kb of the 5'-flanking region, exons, and introns of bovine uromodulin gene was isolated. Transgenic mice containing 3.9 kb of the bovine **uromodulin promoter** and a lacZ reporter gene were generated by pronuclear microinjection. RT-PCR and northern blot analyses of transgene expression in various tissues of founder and F1 mice showed that the transgene was expressed exclusively in the kidney. In situ hybridization and histochemistry for lacZ demonstrated that transgene expression was restricted to tubule epithelial cells of the loop of Henle in the kidney. Stepwise 5' deletion analysis revealed that transfection of luciferase reporter constructs fused to various proximal 5'-flanking regions of the bovine uromodulin gene markedly increased luciferase activity in mouse renal epithelial cells but not in mesenchymal cells and that the most critical cis elements of the uromodulin gene are located within the 600 bp upstream region.

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